REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office action dated September 10, 2002 are respectfully requested. Applicants petition the Commissioner for a 1-month extension of time. A separate petition accompanies this amendment.

Attached hereto is a marked-up version of the changes made to the specification and claims. The attached pages are captioned **"Version with markings to show changes made."**

I. Amendments

Claim 30 has been amended in accord with the Examiner's kind suggestion to add a comma between "distearoylphosphatidylcholine" and "sphingomyelin".

Claim 31 has been amended to clarify that the cationic lipid is shielded by the hydrophilic polymer chains.

Claim 37 has been amended to provide proper antecedent basis.

The claim amendments add no new matter.

II. Rejections under 35 U.S.C. §112, second paragraph

Claims 30-33, 37-39, and 58-59 were rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner had four specific objections which are set forth and addressed below.

1. Rejection of Claim 30: The Examiner objected to the claim as allegedly needing a comma between "distearoylphosphatidylcholine" and "sphingomyelin".

Applicants have amended claim 30 in accord with the Examiner's kind suggestion.

2. Rejection of Claim 31: The Examiner objected to the language "shielded cationic lipid to impart a positive liposome-surface charge" as allegedly unclear what the Applicants intend to convey.

Applicants have amended claim 31 to clarify that the cationic lipid is shielded by the hydrophilic polymer chains.

3. Rejection of Claim 37: The Examiner objected to the language "the hydrophilic polymers" for antecedent basis.

Applicants have amended claim 37 to clarify that it is "hydrophilic polymer chains" that are joined by a chemically releasable bond.

4. Rejection of Claim 58: The Examiner objected to the claim as allegedly unclear as to the location of the diblock polymer as recited in relation to the hydrophilic polymer recited in claim 29.

Applicants respectfully direct the Examiner to page 10, lines 1-12 and 26-30 where a description of both the hydrophilic polymer chains and the diblock copolymer is given. Applicants further respectfully direct the Examiner to Figure 1 which depicts a liposome having a coating of hydrophilic polymer chains (for example, reference character 18) and a diblock copolymer (for example, reference character 16).

Accordingly, withdrawal of the rejections under 35 U.S.C. § 112, second paragraph is respectfully requested.

III. Rejections under 35 U.S.C. §102

Claims 29-31, 33-37, 39, and 40-45 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Marshall *et al.* (U.S. Patent No. 5,939,401).

These rejections are respectfully traversed for the following reasons.

A. The Invention

The present invention relates to a method of administering a therapeutic agent entrapped in liposomes formed of vesicle-forming lipids and having a coating of hydrophilic polymer chains on the liposome outer surface via inhalation.

B. The Cited Art

MARSHALL *ET AL.* relate to cationic amphiphiles complexed with therapeutic molecules for intracellular delivery. The cationic amphiphiles are mixed with a biologically active molecule to form a complex consisting of the amphiphile and the molecule. In Example 6,Marshall *et al.* describe aerosolized delivery of complexes stabilized with PEG-DMPE to the lung.

C. Analysis

The standard for lack of novelty, that is, for anticipation, is one of strict identity. To anticipate a claim for a patent, a single prior source must contain all its essential elements. M.P.E.P. § 2131

As embodied by claim 29, the present invention includes administering, via inhalation, liposomes formed of vesicle-forming lipids and having a coating of hydrophilic polymer chains on the liposome outer surface, where said liposomes have an entrapped therapeutic agent.

The teaching of Marshall *et al.* fails to show at least the following presently claimed elements: (1) a liposome; (2) a liposome having a coating of hydrophilic polymer chains; and (3) a liposome having an entrapped therapeutic agent.

With respect to the first element, it is clear from the teaching in Marshall *et al.* that discrete liposomes are not formed with the cationic amphiphiles. The cationic amphiphiles form "complexes" rather than liposomes, as evidenced by the following description in the Marshall *et al.* document:

1. On Col. 15, lines 19-26, Marshall *et al.* describe preparing a dispersion of a cationic amphiphile; contacting the dispersion with a biologically active molecule to form a complex between said amphiphile and said molecule.

2. On Col. 33, lines 33-49, Marshall *et al.* states that while cationic amphiphiles can form liposomes, "the cationic amphiphiles of the invention need not form highly organized vesicles in order to be effective, and in fact can assume (with the biologically active molecules to which they bind) a wide variety of loosely organized structures."

3. On Col. 33, lines 62-65, Marshall *et al.* state "owing to the potential for leakage of contents therefrom, vesicles or other structures formed from numerous of the cationic amphiphiles are not preferred by those skilled in the art in order to deliver low molecular weight biologically active materials."

These comments are consistent with the thermodynamic expectation that mixing a negatively charged biologically active molecule with a cationic amphiphile will initially result in charge-charge interaction between the two species. A loose, nonordered complex of the two species will form. Upon neutralization of the charge, and in the presence of any excess cationic amphiphiles, bilayer formation around the entire complex can occur. However, mere presence of a bilayer does not imply liposome formation, since a liposome is considered to those of skill in the art to be a discrete, defined particle.

This view is supported by the disclosure of Marshall *et al.* on Col. 53, lines 46-50, where PEG-DMPE is added to "stabilize" the cationic amphiphile-molecule complex, "preventing further aggregation of formed amphiphile/DNA complexes." Were liposomes formed by the cationic amphiphile complex, aggregation would not be a problem since liposomes are stable, discrete particles with little tendency to aggregate.

The disclosure by Marshall *et al.* on Col. 33, lines 62-66 stating that vesicles or other structures (e.g., other than complexes) formed from numerous of the cationic amphiphiles are not preferred because of leakage of the entrapped contents is consistent with Applicants' assertion that liposomes are not formed from the cationic amphiphiles. Liposome formation requires that the lipids have the ability to pack into spherical particles and leakage of entrapped small molecular weight content indicates lack of ability to pack appropriately for true liposome formation.

Marshall et al. further fail to teach a liposome having a coating of hydrophilic polymer chains on the liposome outer surface. For the reasons given above, Marshall *et al.* fail to teach a liposome in general and thus cannot be said to teach a liposome with a coating of hydrophilic polymer chains. Even if the cationic amphiphiles were said to form liposomes, Marshall *et al. does not teach use of a lipid-PEG conjugate for liposome formation. In Marshall* et *al., the sole disclosure of lipid-PEG conjugate is for stabilization*

of a complex of a DNA-cationic amphiphile. Thus, there is no disclosure of a liposome having a coating of polymer chains.

Marshall et al. *also fail to teach* a liposome having an entrapped therapeutic agent. For the reasons given above, Marshall *et al.* fail to teach a liposome in general and thus cannot be said to teach a liposome with an entrapped agent. It is imminently clear from the disclosure of Marshall *et al.*, and well supported in the literature, that polynucleotides cannot be "entrapped" in liposomes due to the large size. Moreover, when cationic lipids are used for liposome formation, the charge interaction of the lipids with the polynucleotides inhibits liposome formation and entrapment of the agent. With respect to the disclosure in Marshall *et al. on entrapping small molecules, Marshall* et al. *admits that small molecules leak from the structure formed, and thus there cannot be an entrapped therapeutic agent.*

Therefore, since the disclosure of Marshall *et al.* fails to teach all of the claimed elements, the standard for novelty has not been satisfied. Withdrawal of the rejection under 35 U.S.C. §102 is respectfully requested.

III. Rejections under 35 U.S.C. §103

Claims 29-30, 34-37, 39-41, 44-49, and 55 were rejected under 35 U.S.C. §103 as allegedly obvious over Mihalko *et al.* (PCT Publication No. WO 86/06959 to Liposome Technology) in combination with Klibanov *et al.* (J. Liposome Research, 2(3):321-334, 1992).

Claims 29-31, 33-37, 39, and 40-45 were rejected under 35 U.S.C. §103 as allegedly obvious over Marshall *et al.* by itself or in combination with Mihalko *et al.*

Claims 31-33 were rejected under 35 U.S.C. §103 as allegedly obvious over Marshall *et al.* by itself or in combination with Mihalko *et al.*, further in view of Gao and Huang (*BBRC*, 179(1):280-285, 1991).

Claims 49-57 were rejected under 35 U.S.C. §103 as allegedly obvious over Mihalko *et al.* in combination with Klibanov et al, further in view of Chestnut *et al.* (U.S. Patent No. 5,800,815), DeFrees *et al.* (U.S. Patent No. 5,604,207) and Applicants' statements of prior art.

These rejections are respectfully traversed.

A. The Invention

The present invention is described above.

B. The Cited Art

MARSHALL *ET AL.* is described above.

MIHALKO *ET AL.* describe a method and system for inhalation administration of a drug in a suspension of liposomes. Release of the drug from the liposomes is selectively controlled via selection of the liposome lipid composition, where the drug release half-live may range from a half hour or less to six days or more.

KLIBANOV *ET AL.* disclose coating liposome surfaces with a hydrophilic layer to provide a long blood circulation half-life after intravenous administration. The hydrophilic layer shields the liposomes from rapid uptake by the reticuloendothelial system. The liposomes may further comprise an anti-tumor antibody attached (in one embodiment) to the distal ends of PEG chains on liposomes to target the liposomes to a tumor site.

GAO AND HUANG disclose a cationic cholesterol derivative as a nonviral transfection reagent and formation of liposomes with the reagent.

CHESTNUT *ET AL.* disclose compositions and methods for treating inflammation and other conditions using blocking P-selectin antibodies. An anti-P-selectin immunoglobulin may be imbedded in an liposome to target the liposome to P-selectin molecules.

DEFREES *ET AL.* relate to analogues of sialyl Le^x that inhibit cellular adhesion between a selectin and cells that express sialyl Le^x on their surfaces. Liposomes with

an entrapped chemotherapeutic agent can be targeted to a site of tissue injury by the selectin-SLe^x analogue. The analogue is positioned on the surface of the liposome. The liposome is fashioned such that a connector portion is incorporated into the membrane at the time of forming the liposome membrane. The connector portion has a lipophilic portion that is embedded and anchored in the membrane. The liposomes may be administered parenterally or locally.

C. Analysis

As stated in M.P.E.P. § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations."

1. Rejection over Mihalko *et al.* in combination with Klibanov *et al.*

A. No Motivation to Combine

None of the references, or combination of references, provide motivation for combining the references along the lines of the invention. Obviousness requires some logical reason for combining the references at hand; otherwise, the use of the references will entail prohibited hindsight (e.g., Ex parte Stauber, 208 USPQ 945 (1980 BPAI); In re Adams, 356 F2d 998, 148 USPQ 742 (CCPA 1966); In re Imperato, 486 F2d 585, 179 USPQ 730 (CCPA 1973)). In particular, the fact that references can be combined does not make the combination obvious unless the prior art also contains something to suggest the desirability of that combination (In re Imperato, 486 F2d 585, 179 USPQ 730 (CCPA 1973); In re Semaker, 702 F.2d 989, 217 USPQ 1 (CAFC 1983)).

To arrive at the claimed invention, one would need to modify the liposomes of Mihalko *et al.* to include a coating of hydrophilic polymer chains. The Examiner purports to find motivation to make this modification since to "coat the liposomes of WO 86 with a

hydrophilic polymer would have been obvious to one of ordinary skill in the art because such a coating would enable the liposomes to circulate longer and reach the target tissue." (Office action dated September 10, 2002, page 4). This asserted motivation fails for the following reasons.

First, it is clear from the teaching of Klibanov *et al.* that the purpose of providing a coating of hydrophilic polymer chains on a liposome is to extend the blood circulation lifetime of the liposomes. That is, the hydrophilic polymer shields the liposomes from recognition and uptake by the RES (page 324, lines 19-22). However, the liposomes of Mihalko et al. are administered not into the blood circulation where RES uptake is a problem but are administered by inhalation to the lung. Mihalko *et al.*, based on the teaching of Klibanov *et al.*, would find no reason to modify the liposomes to have an extended blood circulation lifetime since blood circulation life is of no concern in inhalation administration.

Nor is motivation for the modification found in the teaching of Klibanov *et al.* Klibanov *et al.* is concerned solely with intravenous administration and nowhere mentions other forms of administration, much less inhalation, or that liposomes with a coating of hydrophilic polymers chains would be useful, suitable, or desirable for inhalation administration.

Accordingly, nothing in the teachings of Mihalko *et al.* or Klibanov *et al.* would motivate one skilled in the art to modify the liposomes of Mihalko *et al.*, that are designed for administration to the lung, with the teaching of the Klibanov *et al.* to provide a coating of hydrophilic polymer chains to extend blood circulation lifetime of intravenously administered liposomes.

B. No Expectation of Success

As noted above, another of the basic criteria to establish a *prima facie* case of obviousness is that "there must be a reasonable expectation of success." Neither of the references, alone or in combination provide a reasonable expectation of success that liposomes having a coating of hydrophilic polymer chains would be effective for administration by inhalation.

One important requirement for successful delivery of liposomes to the lung is particle size. As noted by Mihalko et al. "[r]educing liposome particle size may be important in achieving efficient aerosolization of the liposomes" (page 13, lines 24-26). Coating a liposome with hydrophilic polymer chains increases the spherical volume of the particle[1], counter to the expressly stated requirement of Mihalko *et al.* for efficient administration to the lung. A particle with a larger spherical volume is more difficult to administer to the lung itself and tends to be retained in the upper airway. Thus, in this respect, it would undesirable to coat the liposomes of Mihalko *et al.* with a polymer.

Accordingly, withdrawal of the rejection based on *Mihalko et* al. in view of *Klibanov et* al. under 35 U.S.C. § 103 is respectfully requested.

2. Rejection over Marshall *et al.* by itself or in combination with Mihalko *et al.*

The Examiner alleges that "it would have been obvious to one of ordinary skill in the art to use this mode of administration suggested by Marshall since the mode of administration is the choice of the practitioner. One of ordinary skill in the art would be motivated to use the inhalation route since WO shows the [sic] this route as a successful mode of administration of liposomes." (September 10, 2002 Office action, page 5).

As noted above, Marshall *et al.* is concerned with intracellular delivery and teaches a particular type of lipid, a cationic amphiphile, as a vehicle to achieve intracellular delivery of a compound, particularly a nucleic acid. The cationic amphiphiles when mixed with a nucleic acid form a complex, as opposed to a liposome. Marshall *et al.* discloses that low molecular weight compounds leak from the structure formed by the cationic amphiphiles, suggesting that the cationic amphiphiles are incapable of packing to achieve liposome formation. Moreover, Marshall *et al.* nowhere shows or suggests a liposome having a coating of hydrophilic polymer chains on the liposome outer surface. At most, Marshall *et al.* teaches a nucleic acid-cationic amphiphile complex stabilized with a PEG derivatized lipid.

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[1]Hristova and Needham, in STEALTH LIPOSOMES, Lasic and Martin, Eds., CH 5: "Physical Properties of Polymer-Grafted Bilayers", CRC Press, 1995. Copy enclosed.

Mihlako *et al.* is silent regarding hydrophilic polymer chains and utterly fails to show or suggest coating a liposome with hydrophilic polymer chains. Further, as noted above, Mihalko *et al.* emphasizes the importance of a small liposomes size for aerosolization and delivery to the lung. Addition of polymer chains to the outer surface increases the spherical volume of the liposome. Thus, it would not be obvious based on the teaching in Mihalko *et al.* to add hydrophilic polymer chains to the liposome.

Thus, the teachings of Marshall *et al.* and Mihalko *et al.* fail to show or suggest a method of delivering via inhalation liposomes having a surface coating of hydrophilic polymer chains and an entrapped compound as presently claimed. Accordingly, Applicants respectfully request withdrawal of the rejection over Marshall et *al. alone or in combination with* Mihalko et *al.* under 35 U.S.C. §103.

3. Rejection over Marshall *et al.* by itself or in combination with Mihalko *et al.*, further in view of Gao and Huang

The deficiencies of Marshall *et al.* and Mihalko *et al.* are discussed above. The teachings in Gao and Huang do not make up for this deficiency as Gao and Huang make no mention of hydrophilic polymer chains or of coating a liposome with hydrophilic chains.

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

4. Rejection over Mihalko *et al.* in combination with Klibanov et al, further in view of Chestnut *et al.*, DeFrees *et al.*, and Applicants' statements of prior art

As noted above, any attempt to combine the teachings of Mihalko *et al.* and Klibanov *et al.* fails for lack of motivation to combine and/or a reasonable expectation of success. More specifically, nothing in the teachings of Mihalko *et al.* or Klibanov *et al.* would motivate one skilled in the art to modify the liposomes of Mihalko *et al.*, that are designed for administration to the lung, with the teaching of the Klibanov *et al.* to provide a coating of hydrophilic polymer chains since such chains serve to extend blood circulation lifetime of intravenously administered liposomes and this is not of concern for liposomes delivered by inhalation.

Moreover, Milhalko *et al.* states the importance of small liposome size for inhalation delivery, and to modify liposomes with polymer chains increases the overall spherical volume, expressly in contrast to the teaching in Milhalko *et al.*

The teachings of Chestnut *et al.*, DeFrees *et al.*, and Applicant's statements do not make up for these problems in attempting to combine the teachings of Milhalko *et al.* with Klibanov *et al.* Chestnut *et al.* and DeFrees *et al.* are concerned with liposomes having a targeting ligand on the surface of the liposome. Neither reference makes any reference to a coating of hydrophilic polymer chains on the liposome outer surface or of administration by inhalation. Applicants' statement that targeting ligands are knows also does not make up for the problems in combination of Milhalko *et al.* with Klibanov *et al.*

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

IV. CONCLUSION

In view of the above remarks, Applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

The Examiner is invited to contact Applicants' representative at 650-838-4410 if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

30. (Amended) The method of claim 29, wherein the vesicle-forming lipid is selected from the group consisting of hydrogenated soy phosphatidylcholine, distearoylphosphatidylcholine, sphingomyelin, diacyl glycerol, phosphatidyl ethanolamine, phosphatidylglycerol, distearyl phosphatidylcholine, and distearyl phosphatidylethanolamine.

31. (Amended) The method of claim 29, wherein said liposomes further contain a [shielded] cationic lipid shielded by said coating of hydrophilic polymer chains, said cationic lipid being effective to impart a positive liposome-surface charge.

37. (Amended) The method of claim 29, wherein at least a portion of the hydrophilic polymer[s] chains are joined by a chemically releasable bond.